Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/787256
INTERNATIONAL APPLICATION NO. PCT/EP99/07003	INTERNATIONAL FILING DATE 15 September 1999	PRIORITY DATE CLAIMED 18 September 1998
TITLE OF INVENTION PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE)		
APPLICANT(S) FOR DO/EO/US Jerome Francis HAYES, Timothy Charles WALSGROVE, and Andrew Stephen WELLS		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [X] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [X] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/EP99/07003, filed 15 September 1999, which claims benefit of GB 9820405.0, filed 18 September 1998.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO. (if known see 37 CFR 1.50)	INTERNATIONAL APPLICATION NO.	ATTORNEYS DOCKET NO.
09/787256	PCT/EP99/07003	P32147

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$860.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) **$690.00**	**$690.00**	
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$710.00**		
Neither International Preliminary Examination Fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,000.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$690.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**18- 20 =**	**0**	**0 x $18.00**	**$0.00**	
Independent claims	**2- 3 =**	**0**	**0 x $80.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $270.00**	**$0.00**	
			TOTAL OF ABOVE CALCULATIONS =	**$690.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
			SUBTOTAL =	**$690.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
			TOTAL NATIONAL FEE =	**$690.00**	
			Amount to be refunded	**$**	
			charged	**$**	

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$690.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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37,347
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"EXPRESS MAIL CERTIFICATE"
"EXPRESS MAIL" MAILING LABEL NUMBER EL 300 526 758 US
DATE OF DEPOSIT 15 March 2001

Attorney Docket No. P32147

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07003	15 September 1999	18 September 1998

TITLE OF INVENTION
PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE)

APPLICANT(S) FOR DO/US
Jerome Francis HAYES, Timothy Charles WALSGROVE, and Andrew Stephen WELLS

Box PCT
Assistant Commissioner for Patents
Washington, D.C. 20231
ATTENTION: DO/US

PRELIMINARY AMENDMENT

Sir:

Prior to the first Office Action on the merits, the Applicants request entry of the following amendment.

IN THE CLAIMS:

Please amend claims 4, 6, 7, and 8 to read as follows:

4. (Once Amended) A process according to claim 1 wherein the ratio of water miscible cosolvent : water is in the range 10:1 to 1:2 v/v.

6. (Once Amended) A process according to claim 1 wherein the ratio of 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v.

7. (Once Amended) A process according to claim 1 which uses from 0.7 to 1.5 mole equivalents of methanesulfonic acid.

8. (Once Amended) A process according to claim 1 wherein the recrystallisation solution is seeded with 7-(3-aminomethyl-4-syn-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

Please add new claims 11-18 as follows:

11. (New) A process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises:

(a) reacting 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in solution with a solvent comprising at least one C_{1-4} alcohol and water, wherein from 0.7 to 1.5 mole equivalents of methanesulfonic acid is used, the ratio of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v, and the ratio of C_{1-4} alcohol : water is in the range 10:1 to 1:2 v/v, and

(b) isolating the resulting solid product.

12. A process according to claim 11 wherein the C_{1-4} alcohol is isopropanol.

13 A process according to claim 11 wherein the ratio of C_{1-4} alcohol : water is 2:1 v/v.

14. A process according to claim 11 wherein the recrystallisation solution is seeded with 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

15. A process according to claim 14 wherein the solution is seeded whilst at a temperature of $\geq 25°C$.

16. A process according to claim 14 wherein the solution is seeded whilst at a temperature of about 30°C.

17. 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate prepared by the process of claim 1.

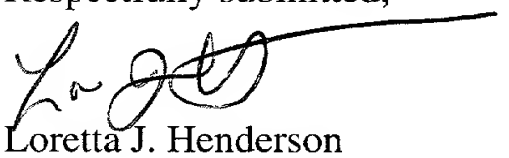
18. 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate prepared by the process of claim 11.

REMARKS

Upon entry of this Preliminary Amendment, claims 1-18 will be pending in the application. Claims 4, 6, 7 and 8 have been amended to delete multiple dependent claim language and to correct an inadvertent typographical error in claim 7. New claims 11-18 are being added. Support for this amendment is found in the claims as originally filed and in the specification at page 2, lines 17-18. No new matter is being added.

Attached hereto is a marked-up version of the changes made to claims 4, 6, 7 and 8 by the current amendment. The attached page is captioned "Version with markings to show changes made."

Respectfully submitted,



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Version with markings to show changes made

Preliminary Amendment to claims 4, 6, 7 and 8 dated March 15, 2001:

4. (Once Amended) A process according to [any one of the preceding claims]claim 1 wherein the ratio of water miscible cosolvent : water is in the range 10:1 to 1:2 v/v.

6. (Once Amended) A process according to [any one of the preceding claims]claim 1 wherein the ratio of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v.

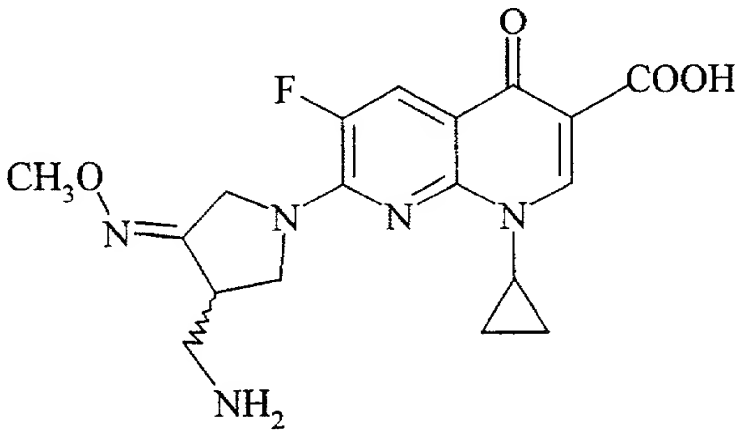
7. (Once Amended) A process according to [any one of the preceding claims]claim 1 which uses from 0.7 to [mole] 1.5 mole equivalents of methanesulfonic acid.

8. (Once Amended) A process according to [any one of the preceding claims]claim 1 wherein the recrystallisation solution is seeded with 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE)

The present invention relates to a process for the production of a naphthyridine carboxylic acid derivative having antibacterial activity.

EP 688772 discloses novel naphthyridine carboxylic acid derivatives, including anhydrous (R,S)-7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid of formula I, having antibacterial activity.



I

WO 98/42705 (published after the priority date of the present application) discloses (R,S)-7-(3-aminomethyl-4-*syn*-methoxyimino-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate and hydrates thereof including the sesquihydrate (the "methanesulfonate sesquihydrate"). WO 98/42705 discloses a process for the production of the methanesulfonate sesquihydrate comprising reaction of the corresponding free base with methanesulfonic acid in dichloromethane / ethanol followed by recrystallisation of the resulting crude salt anhydrate from either water : acetone (10:7 v/v), or water : ethanol (1:2 v/v). The overall yield for this two step process is 70-80%. An alternative process for the production of the methanesulfonate sesquihydrate described in WO 98/42705 comprises exposing a solvate of the methanesulfonate (ethanol 0.11%) to high relative humidity (nitrogen >93% humidity).

The present invention relates to an improved process for the production of the methanesulfonate sesquihydrate which comprises direct salt and hydrate formation.

According to the invention there is provided a process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in a solvent comprising at least one water miscible cosolvent and water, and isolating the resulting solid product.

The 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (hereinafter referred to as "the free base") used in the process of the invention may be prepared as described in EP 688772.

Water miscible cosolvents which may be used in the process of the invention include C_{1-8} alcohols, acetonitrile and dimethylformamide. The water miscible cosolvent is preferably a C_{1-4} alcohol or a mixture thereof, e.g. methanol, ethanol and propanol; the preferred C_{1-4} alcohol is isopropanol.

In addition to at least one water miscible cosolvent and water the solvent may contain other components, such as C_{1-4} haloalkanes. However, the solvent preferably comprises essentially of a water miscible cosolvent and water.

Suitable ratios of water miscible cosolvent : water for use in the process of the invention include ratios in the range 10:1 to 1:2 v/v, preferred ratios are in the range 10:1 to 1:1 v/v, more preferably a ratio of water miscible cosolvent : water of 2:1 v/v is used.

Any suitable ratio of free base to solvent may be used, for example, a ratio of up to 1:100 w/v, particularly a ratio of about 1:9 w/v.

The process of the invention may suitably use from 0.7 to >3 mole equivalents of methanesulfonic acid, preferably 0.7 to 1.5 equivalents, more preferably 0.9 to 1.5 equivalents, especially about 1.0 equivalent of methanesulfonic acid (based on the free base).

The mixture of the free base and methanesulfonic acid may be warmed in the solvent to aid dissolution. On cooling the methanesulfonate sesquihydrate will crystallise out of solution. To aid crystallisation the solution may be seeded with a small quantity of solid methanesulfonate sesquihydrate. In order to obtain polymorphically pure methanesulfonate sesquihydrate it is preferable that seeding of the solution is completed before crystallisation begins. Seeding of the crystallisation solution is preferably performed at a temperature $\geq 25°C$, for example at a temperature of about 30°C.

The process of the invention may be used to produce racemic methanesulfonate sesquihydrate or may be used for the production of enantiomerically enriched or enantiomerically pure methanesulfonate sesquihydrate, using racemic or enantiomerically enriched or enantiomerically pure free base. Enantiomerically enriched or enantiomerically pure free base may be prepared by resolution of the racemic free base, e.g. by chiral HPLC.

The process according to the invention has the advantage that direct salt formation eliminates one step in the synthesis and gives a high yield of high purity methanesulfonate sesquihydrate. In turn these advantages result in improved throughput and savings in labour and materials costs during manufacture.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication

were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following example. However, it should be understood that the example is intended to illustrate but not in any manner limit the scope of the invention.

Example 1 : Preparation of the methanesulfonate sesquihydrate

To a suspension of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (20.00 g, 51.4 mmol) in isopropanol (120 ml) and water (60 ml) was added methanesulfonic acid (3.300 ml, 50.9 mmol) at 38-40°C. The resultant dark brown solution was stirred for 15 min after which time charcoal (6.00 g of Darco G-60) was added. The suspension was stirred at 38-40°C for 4h then filtered. The filtrate was allows to cool to 30°C and seed crystals of (R,S)-7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate (15 mg) added. A precipitate began to form within 15 min. The suspension was allowed to cool to 20-23°C over 90 min and was stirred for 36h. The slurry was cooled to 0-5°C for 60 min then filtered and washed with isopropanol (50 ml and 44 ml). The product was sucked dry for 30 min and then further dried at 50-55°C under vacuum. The dried product was exposed to the atmosphere for 18h to give the methanesulfonate sesquihydrate 21.29 g (85%), purity >99.5% by HPLC.

The X-ray diffraction pattern of the methanesulfonate sesquihydrate was measured as follows:

Diffractometer type:	PW1710 BASED
Tube anode:	Cu
Generator tension [kV]:	40
Generator current [mA]:	30
Wavelength Alpha1 [Å]:	1.54060
Wavelength Alpha2 [Å]:	1.54439
Intensity ratio (alpha1/alpha2):	0.500
Divergence slit:	AUTOMATIC
Irradiated length [mm]:	12
Receiving slit:	0.1
Spinner:	ON
Monochromator used:	YES
Start angle [°2θ]:	3.500
End angle [°2θ]:	35.000
Step size [°2θ]:	0.020

Maximum intensity:	2970.250
Time per step [s]:	2.300
Type of scan:	STEP
Minimum peak tip width:	0.10
Maximum peak tip width:	1.00
Peak base width:	2.00
Minimum significance:	0.50

The X-ray diffraction pattern of the methanesulfonate sesquihydrate is shown in Figure 1. The compound shows characteristic peaks at 2θ = 8.2, 12.2 and 14.6°.

CLAIMS

1. A process for the production of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate which comprises reacting 7-(3-aminomethyl-4-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and methanesulfonic acid in a solvent comprising at least one least one water miscible cosolvent and water, and isolating the resulting solid product.

2. A process according to claim 1 wherein the water miscible cosolvent is a C_{1-4} alcohol.

3. A process according to claim 2 wherein the water miscible cosolvent is isopropanol.

4. A process according to any one of the preceding claims wherein the ratio of water miscible cosolvent : water is in the range 10:1 to 1:2 v/v.

5. A process according to claim 4 wherein the ratio of water miscible cosolvent : water is 2:1 v/v.

6. A process according to any one of the preceding claims wherein the ratio of 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid : solvent is up to 1:100 w/v.

7. A process according to any one of the preceding claims which uses from 0.7 to mole 1.5 equivalents of methanesulfonic acid.

8. A process according to any one of the preceding claims wherein the recrystallisation solution is seeded with 7-(3-aminomethyl-4-*syn*-methoxyiminopyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate sesquihydrate to aid crystallisation.

9. A process according to claim 8 wherein the solution is seeded whilst at a temperature of $\geq 25°C$.

10. A process according to claim 9 wherein the solution is seeded whilst at a

temperature of about 30°C.

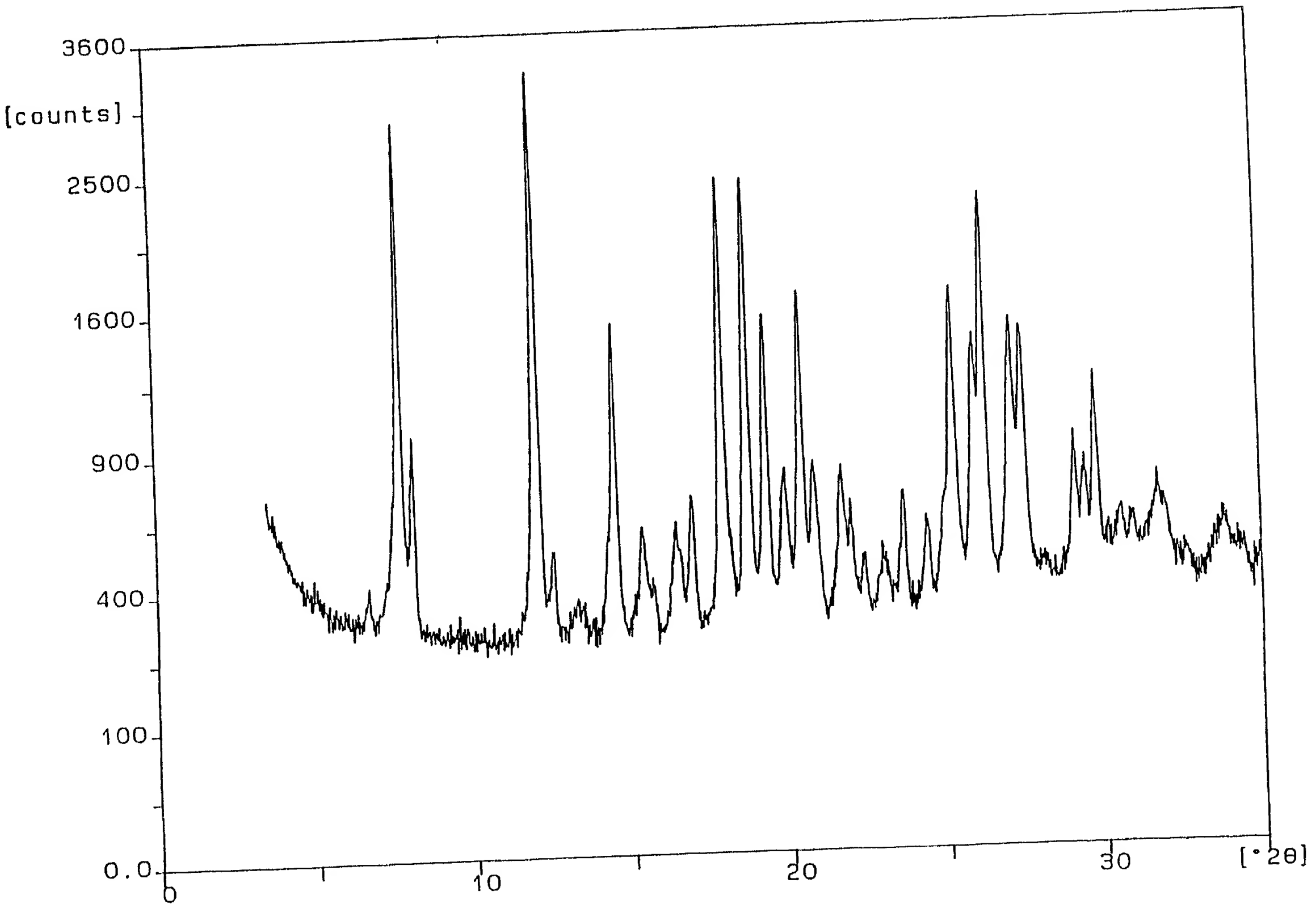
P32147

ABSTRACT

A PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE

A process for the production of a naphthyridine carboxylic acid derivative having antibacterial activity.

FIGURE 1



WO 00/17199
1/1
PCT/EP99/07003
09/762,259

Docket No.: P32147 PCT/EP99/07003

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

PROCESS FOR THE PRODUCTION OF A NAPHTHYRIDINE CARBOXYLIC ACID DERIVATIVE (METHANESULFONATE SESQUIHYDRATE)

the specification of which (check one)

[ ] is attached hereto.

[X] was filed on 15 September 1999 as Serial No. PCT/EP99/07003
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9820405.0	GB	18 September 1998	Yes

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

Customer Number 20462.

Address all correspondence and telephone calls to Edward R Gimmi , SmithKline Beecham Corporation, Corporate Intellectual Proprety-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-4478.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's Signature: _____ Date: 20th February 2001

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200

Full Name of Inventor: Timothy Charles WALSGROVE

Inventor's Signature: Timothy Charles Walsgrove Date: 20-FEB-01

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Citizenship: British

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300 Full Name of Inventor: Andrew Stephen WELLS

Inventor's Signature: A Wells Date: 5 March 2001

Residence: Quorn, Leicestershire, United Kingdom GBX

Citizenship: British

Post Office Address: GlaxoSmithKline
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